Please check all that are applicable:

☐ I am an adult participant in this study.

Print your name here: _____

☐ I am the parent or guardian granting permission for a child in this study (the use of "you" refers to "your child" or "your ward.")

Print child's name here: _____

Are you participating in any other research studies? _____ Yes _____No

INFORMED CONSENT/PARENTAL PERMISSION TO PARTICIPATE IN A RESEARCH STUDY

If you are a parent or legal guardian of a child who may take part in this research study, permission from you is required and we may request the assent (agreement) of your child. When the word "you" appears in this consent form, it refers to you, your son, or daughter.

KEY INFORMATION TO CONSIDER

1. **You are being asked to take part in a research study. Research studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.**

2. **Research Summary**

   - The purpose of this study is to find out what effects, good and/or bad, treatment with a new combination of drugs, cyclophosphamide, etoposide, and carfilzomib has on you and your cancer.

   - In this clinical trial, we are looking at the use of carfilzomib in combination with cyclophosphamide and etoposide for children with relapsed/refractory solid tumors or leukemia.

   - The combination of drugs, cyclophosphamide, etoposide, and carfilzomib will initially be given on Days 1-5 of every cycle. Each cycle will be 28 days long. If you show a response to treatment, have recovered from the side effects, your organs are

working well and your lab tests are acceptable, you will be able to receive another cycle.

3. Foreseeable Risks or Discomforts

You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib in the section below titled "What are the risks of this study?". However, your doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. There may be serious unexpected or unforeseen risks while taking carfilzomib, including death. It is known that nearly everyone who takes carfilzomib will have some side effects while on the drug. Many of these side effects may be mild, but some side effects can be serious and even fatal.

4. Expected Benefits

If you agree to take part in this study, there may or may not be a direct medical benefit to you. We hope the information learned from this study will benefit other patients with relapsed/refractory tumors or leukemia in the future.

5. Alternative Course of Treatment

You do not have to participate in this research study to receive treatment for your cancer. Before signing this informed consent document, the study doctor will talk to you about other treatments or therapies that are available for you.

PURPOSE OF RESEARCH

Introduction

INVITATION TO PARTICIPATE you = you and/or your child
You are being asked to take part in this research study because you have either a tumor or leukemia that is not responding to treatment.

This is a Phase I research study. In this clinical trial, we are looking at the use of carfilzomib in combination with cyclophosphamide and etoposide for children with relapsed/refractory solid tumors or leukemia. Carfilzomib is FDA (Food and Drug Administration) approved in the United States for adults with multiple myeloma (a type of cancer). However, this drug is not approved for the disease for which you are being treated in this study. Since carfilzomib has not yet been used in children to treat this condition, we must first find the best dose to give. We are looking for the highest dose of carfilzomib that can be given safely. Therefore, not all children taking part in this study will receive the same dose of the study drug in the first part of the trial.

The medications cyclophosphamide and etoposide are standard drugs often used together for the treatment of cancer in children with solid tumors or leukemia.

To allow you to make an informed decision as to whether or not you want to take part in this research study, this document describes the purpose of the study, your rights and obligations, the procedures needed by the study, and the possible benefits and risks of participating in the study. Please take time to read the following information carefully. Feel free to talk with your doctor, nurse, family, or friends before deciding. If you decide to terminate your participation in this study, you should notify Dr. Lacayo at (650) 497-8953.

What is the purpose of the study?
The purpose of this study is to find out what effects, good and/or bad, treatment with a new combination of drugs, cyclophosphamide, etoposide, and carfilzomib has on you and your cancer and what the best dose of carfilzomib is for children.

In part 1 of the trial, small groups of children will be enrolled in steps. The first group will be given a certain dose of carfilzomib. If these children do not have side effects which are too bad, the next small group of children enrolled will receive a higher dose. This increase in doses with groups of people will continue until we find the highest dose of the drug that can be given without causing severe or unmanageable side effects. If you are eligible for part 1 of the study and you choose to take part in it, the dose of study drug you receive will depend on the number of people who enroll in this study before you. It will also depend on how well they tolerate their doses of the study drug.

The study doctor will tell you what dose you will receive and how this compares to the doses given to other children in the study. As this part of the study is designed to find the maximum tolerated dose of carfilzomib, the dose you will receive might not be enough to take care of your illness, or it might be too high and cause harmful side effects. Your doctor will discuss the potential side effects with you in further detail.

Part 2 of this study will enroll additional patients at the highest tolerable dose found in Part 1 in order to get more information on side effects and make sure the dose is tolerable. However, commencement of Part 2 will be at the discretion of the Principal Investigator and may be discontinued due to subject safety or enrollment barriers.

Who has reviewed this research?
This study has been approved by Stanford IRB, an organization that is responsible for protecting the rights and safety of patients who take part in research studies.

How many people will take part in the study?
Approximately 50 children, teenagers, and young adult patients will take part in this study. This study is organized by POETIC, a consortium of 10 Hospitals in North America that conducts clinical trials for children with cancer. Stanford University expects to enroll 5-10 research study

participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

PROCEDURES

What will happen if I take part in this research study?

SCREENING ASSESSMENTS

During the screening period, the study doctor will find out if you qualify for this study. This period may last up to 14 days and may involve more than one visit to the clinic.

Before you begin the study, you will need to undergo the following tests or procedures to find out if you can be in the study. Some of these tests or procedures may be part of your regular medical care and may be done even if you do not take part in the study. If you have had some of them recently, they may not need to be repeated. Your study doctor will tell which of these you must do.

- Discussion of this study and review and signing of this Informed Consent Form, and if applicable, Child Assent
- Recording of your demographic information, including age, sex, and race/ethnicity as permitted by local regulatory authorities
- Review of your medical history and any medications (including herbal medications, over-the-counter medications, or dietary supplements) you have taken within the last 14 days
- Complete physical examination, including Tanner staging (which says how sexually mature you are)
- Height and Weight
- Evaluation of performance status (your ability to perform everyday tasks)
- Measurement of your vital signs (blood pressure, pulse rate, breathing rate, blood oxygen levels, and body temperature)
- Electrocardiogram: An electrocardiogram is a test that checks for problems with the electrical activity of your heart
- Echocardiogram: An echocardiogram is a test using sound waves that measures the activity of the heart
- Tumor assessment: determination of your tumor size and location by one or more standard scanning methods chosen by your physician. These include:
    1. Computed tomography (CT) scan, a special x-ray of the body.

2. MRI (magnetic resonance imaging), a scan that is performed using magnetic tools.
3. FDG-PET (fluorodeoxyglucose–positron emission tomography) scan: This is a test that can be used to monitor your cancer. It measures metabolic activity or how much fuel cells need to grow and divide through the measurement of the amount of radioactive glucose used by the tumor. Sometimes this test can tell your doctor sooner than a CT or MRI scan what is going on with your cancer.
4. MIBG scan (if you have a neuroblastoma). This is a special scan for neuroblastoma patients that uses a radioactive tracer called MIBG (a special dye given through an injection into the vein) to identify tumor that may not be seen on CT or MRI scan.

- Collection of cerebrospinal fluid to look for cancer cells
- Bone marrow aspirate/biopsy
- Blood tests: Approximately 1 tablespoon of blood will be drawn for the following laboratory tests (or less depending on your size, as determined by your treatment team):
- Hematology: to check your blood cell counts (for example, anemia or white blood cells)
- Chemistry: to measure your general health and how well your liver, kidneys, thyroid, and other organs are functioning
- Coagulation: tests to check how quickly your blood clots
- Pregnancy test (blood) for female patients who have undergone puberty
- Collection of a urine sample for standard laboratory tests

STUDY TREATMENT

Initial Dosing

The combination of drugs, cyclophosphamide, etoposide, and carfilzomib will initially be given on Days 1-5 of every cycle. Each cycle will be 28 days long. If you show a response to treatment after the first cycle and have recovered from the side effects and meet organ function and laboratory test criteria, you will be allowed to receive another cycle. The next cycle will begin on Day 29-31 of the previous cycle. There is no maximum number of cycles you can receive. The number of cycles will be up to the study doctor and how you are responding to treatment.

In the first 3-6 patients taking part in this study, the dose of carfilzomib will be a low dose. If there are bad effects in these patients, the doses of cyclophosphamide and etoposide will be decreased in the next patients taking part in this study.

If a patient experiences a bad effect, then a single dose de-escalation (lowering) will be allowed for other cycles.

Dosing of the Days 1-5 cycle will begin at Dose Level 1.

Dose Level	Cyclophosphamide mg/m^2	Etoposide mg/m^2	Carfilzomib mg/m^2

-2	See twice weekly dosing schedule (see below)		
-1	330	75	11
1	440	100	11
2	440	100	15
3	440	100	20
4	440	100	20/27*
5	440	100	20/36*

*For the **first cycle only**, patients on dose levels 4 and 5 will receive 20 mg/m^2 on days 1 and 2. Then they will receive either 27 mg/m^2 (level 4) or 36 mg/m^2 (level 5) on days 3 – 5. For all **subsequent cycles**, patients will receive 27 mg/m^2 or 36 mg/m^2 on days 1 – 5.

During Days 1-5, all three drugs will be given in the following order:

- Hour 0-1 Cyclophosphamide given into a vein (intravenously)
- Hour 1-3 Etoposide given into a vein (intravenously)
- Hour 3-3.5 Carfilzomib given into a vein (intravenously)

If you have acute leukemia or non-hodgkin's lymphoma (NHL), you will receive a single dose of intrathecal (IT -into the spinal canal) chemotherapy within 14 days of starting treatment. This chemotherapy is either IT Methotrexate or IT Cytarabine (depending on your diagnosis). The medications methotrexate and cytarabine are standard drugs often given intrathecally for treatment of leukemia.

Twice Weekly Dosing

If dose de-escalation is required below Dose Level -1 on the 5-day dosing schedule shown above, then the study will switch to a 2-day dosing schedule shown below.

Dosing of the 2-day schedule will begin at Dose Level 1.

Dose Level	Cyclophosphamide mg/m^2	Etoposide mg/m^2	Carfilzomib mg/m^2
-2	330	75	15
-1	330	75	20
1	330	75	20/27*
2	440	100	20/27*
3	440	100	20/36*
4	440	100	20/45*
5	440	100	20/56*

*For the **first cycle only,** patients at dose levels 1 to 5 will receive 20 mg/m^2 on days 1 and 2. Then, they will receive either 27 mg/m^2 (levels 1 and 2), 36 mg/m^2 (level 3), 45 mg/m^2 (level 4), or 56 mg/m^2 (level 5) on days 8, 9, 15, and 16. For all subsequent cycles, patients will receive 27 mg/m^2, 36 mg/m^2, 45 mg/m^2, or 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16.

During Days 1-2, cyclophosphamide, etoposide, and carfilzomib will be given in the following order:

- Hour 0-1 Cyclophosphamide given into a vein (intravenously)
- Hour 1-3 Etoposide given into a vein (intravenously)
- Hour 3-3.5 Carfilzomib given into a vein (intravenously)

During Days 3-5, cyclophosphamide and etoposide and will be given in the following order:

- Hour 0-1 Cyclophosphamide given into a vein (intravenously)
- Hour 1-3 Etoposide given into a vein (intravenously)

Days 8, 9 ,15,16 – Carfilzomib alone will be given:

- Days 8, 9 ,15,16- Carfilzomib given into a vein (intravenously) alone over 30 min

If you have acute leukemia or non-hodgkin's lymphoma (NHL), you will receive a single dose of intrathecal (IT -into the spinal canal) chemotherapy within 14 days of starting treatment. This chemotherapy is either IT Methotrexate or IT Cytarabine (depending on your diagnosis).

ASSESSMENTS DURING THE STUDY

Before the first treatment and during each cycle, tests will be done to check your condition. They are part of regular cancer care. A routine physical examination and laboratory tests will be performed. After Cycle 1 of treatment has been given, you will have a disease evaluation performed to find out whether your cancer has responded to treatment. If your cancer has continued to grow (disease progression), you will be removed from the study and other options for treatment will be discussed with you. If your cancer stops growing (stable disease) or responds to treatment, you may continue to receive treatment as long as your cancer continues to respond, and if you did not have any bad side effects that are not tolerable from the treatment.

The schedule of assessments and procedures you may undergo are listed in the following table:

Procedure	Pre-study	Cycle 1						Additional cycles		Final visit
		Day 1	Days 2, 3, 4, 5	Day 8	Day 15	Day 22	Day 28	Day 1	Day 28	
Medical history	X	X						X		X
Physical exam	X	X	X	X	X	X	X	X	X	X
Blood work	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X					X		X
Vital Signs with Pulse oximetry	X	X	X	X	X	X	X	X	X	X
Serum pregnancy	X							X		
Tumor assessment	X								X	
Bone marrow aspirate/biopsy	X						X		X	X
CSF Count	X							X		
EKG & ECHO	X									

DURATION OF STUDY INVOLVEMENT

How long will I be on the study?
The total time you will be on the study treatment will depend on if you have any bad side effects, and how your cancer is responding to treatment. Your doctor may have you stop taking carfilzomib or take a lower dose of carfilzomib because of the side effects, or the side effects may go away on their own even if you continue to take carfilzomib. You may continue indefinitely after that as long as your doctor feels the treatment is safe and is working. You will be followed for 30 days after you stop study treatment to check on the status of your cancer and see what other medications you are receiving for your cancer.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep all study appointments and complete all study assessments
    - If you cannot attend an appointment, please contact study personnel (i.e., the study doctor or research staff) as soon as possible to schedule a new appointment.
- Inform study personnel about any symptoms, changes in medications, doctor's or nurse's appointments, or hospital admissions that you may have had
- Agree to not participate in any other research study
- Inform study personnel if you believe you or your partner might be pregnant
- Inform study personnel if you change your mind about participating in the study
- Inform your other doctors that you are taking part in this study
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

Can I stop being in the study?

Yes. You can decide to stop participating at any time. Tell the study doctor if you are thinking about stopping or decide to stop. The study doctor will tell you how to stop safely.

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability

to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Lacayo at (650) 497-8953.
The Protocol Director may also withdraw you from the study and the study medication may be stopped, without your consent for reasons that include but not limited to the following:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- You need a treatment that is not allowed in the study
- The study has been cancelled
- Pregnancy
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

What are the risks of this study?

Carfilzomib Risks
Carfilzomib is approved by the U.S. Food and Drug Administration (FDA) to be used only in adults with relapsed and refractory multiple myeloma that have tried and failed other therapies. It has not been approved to be used for any other disease or condition. In this study, carfilzomib is an investigational study drug because it is not approved for use in all patients in the United States, and it is not approved by some regulatory authorities (the agencies that are responsible for approving the use of a medicine in a country such as the European Medicines Agency and Health Canada). It has not previously been used in children.

You will be told about the known risks, which are the side effects reported previously by others who took carfilzomib. However, your doctors do not know all the side effects that you may experience. As with all investigational drugs, all risks may not have been identified at this time. There may be serious unexpected or unforeseen risks while taking carfilzomib, including death. It is known that nearly everyone who takes carfilzomib will have some side effects while on the drug. Many of these side effects may be mild but some side effects can be serious and even fatal.

Everyone taking part in the study will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

If side effects occur, your health care team may give you medicines to help lessen side effects.

Information provided below is based on data from approximately 6500 patients who took carfilzomib while taking part in clinical studies. During this time period the following side effects have been observed and may be due to carfilzomib.

The known and potential risks for **Carfilzomib** associated with the study under investigation for your condition may include, but are not limited to:

- Likely (greater than 20% chance of occurring)
- Less Likely (5-20% chance of occurring)
- Rare but serious (less than 5% chance of occurring)

Risks and side effects related to Carfilzomib include those which are:
The frequencies of these side effects are approximate only.

Likely *(occurs in more than 20 out of 100 patients)*

- Fatigue (tiredness)
- Fever
- Headache
- Cough
- Shortness of breath (at rest or with exertion) which in rare cases may be life-threatening or resulting in death
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased red blood cell count which may lead to feeling tired
- Decreased platelet counts which may lead to increase bleeding or bruising
- Decreased white blood cell count which may decrease your ability to fight infection
- Respiratory tract infection
- Swelling of the hands, feet or ankles
- Back pain
- Stomach pain, discomfort, or swelling
- General weakness
- Chills
- Pneumonia
- Loss of or decreased appetite which may lead to weight loss
- Pain in the bones or joint pain
- Pain in limbs, hands or feet
- Muscle spasms
- Dizziness
- Insomnia (difficulty sleeping)
- Increase in blood pressure
- Changes to blood tests (decreased blood levels of potassium and/or magnesium, increased blood levels of sugar and/or creatinine)
- Numbness, tingling, or decreased sensation in hands and/or feet
- Infusion reactions (which can occur during or shortly after carfilzomib infusion) including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, and low blood pressure
- Runny nose or nasal congestion

Less Likely *(occurs in 5–20 out of 100 patients)*

- Anxiety
- Decrease white blood cell count, which may be with fever
- Confusion or changes in mental state
- Blurred or double vision
- Eye cataract
- Blood chemistry and electrolyte alterations
- Redness of the skin
- Pain, burning, or irritation at the infusion site
- Generalized pain
- Increased sweating
- Chest pain

- Heart failure, and heart problems including rapid, strong, or irregular heartbeat
- Blood clot in the lungs
- Fluid in the lungs
- Muscle spasm, pain, or weakness
- Indigestion (upset stomach)
- Inflammation of the liver (mild, reversible changes in liver function tests)
- Urinary tract infection
- Nosebleeds
- Dehydration
- Sore throat, inflammation of the nose and throat
- Change in voice or hoarseness
- Decrease in blood pressure
- Bronchitis
- Toothache
- Flu-like symptoms such as fever, chills, or shaking that may occur at any time but are more likely to occur on the day of or the day after carfilzomib infusion.
- Serious infection in the blood (sepsis)
- Viral infection
- Kidney problems, including decreased ability to make urine, increased creatinine in the blood, and kidney failure needing dialysis
- Changes to blood tests (decreased blood levels of sodium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, or c-reactive protein)
- Blood clots in the veins
- Infusion site reaction (pain, redness or swelling where you received the injection into your vein)
- Wheezing
- High blood pressure in lungs (pulmonary hypertension)

Rare but Serious (occurs in less than 5 out of 100 patients)

- Worsening liver function up to and including liver failure
- Itchy skin, yellow skin, very dark urine and very pale stools which may be caused by a blockage in the flow of bile from the liver (cholestasis)
- Multi-organ failure
- Decreased or worsening of heart function including chest pain, abnormal heart rhythm, heart attack.
- Abnormal amount of fluid between the heart and lining around the heart
- Swelling and irritation of the lining around the heart
- Perforation in stomach, small intestine or large bowel
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombocytopenic Thrombotic Purpura/Haemolytic Uremic Syndrome (TTP/HUS)
- Tumor lysis syndrome (TLS) - Tumor lysis syndrome is caused by rapid killing of tumor cells during treatment. When the tumor cells die, they release their contents into the bloodstream. If cell killing is very rapid, this can affect blood chemistries and the kidneys. In severe cases, this can lead to shutdown of kidney function requiring dialysis.
- Myelodysplastic syndromes (MDS)/ Acute Myeloid Leukemia (AML) - Myelodysplastic syndromes refers to a disorder that develops when the cells in the bone marrow (the soft inner part of the bones, where new blood cells are made) do not work properly and have problems making new blood cells. A person with MDS may experience no

symptoms or may experience fatigue, infection, easy bruising or bleeding. MDS can turn into a cancer of bone marrow cells called acute myeloid leukemia (AML).
- Posterior reversible encephalopathy syndrome (PRES) is a rare condition that causes swelling of the brain and affects how it functions. A person with PRES may experience headaches, confusion, loss or decreased level of consciousness, blurred vision or blindness, seizures, and possibly death. If caught early and treated, PRES may be reversed.
- Extremely high blood pressure (Hypertension including hypertensive crises)
- Lung disorders (Pulmonary toxicities such as Interstitial Lung Disease (including pneumonitis), Acute Respiratory Failure and Acute Respiratory Distress Syndrome (ARDS))
- Hepatitis B Virus (HBV) reactivation, a serious liver infection that may come back if you already had HBV
- Acute pancreatitis (inflammation of the pancreas)
- Intestinal (bowel) obstruction
- Stroke (Cerebrovascular accident)
- Thrombotic microangiopathy
- Allergy to carfilzomib
- Cytomegalovirus chorioretinitis - Infection of the back of the eye
- Laryngeal edema- Swelling of the throat
- Progressive Multifocal Leukoencephalopathy (PML) - a viral infection that may cause clumsiness, trouble speaking, partial blindness and impaired brain function
- Inflammation of the pancreas (acute pancreatitis)
- Intestinal (Bowel) obstruction

*There is an increased risk of heart failure in Asian-Pacific (China, Japan, Taiwan, Singapore, Republic of Korea, and Thailand) patients treated with carfilzomib.

You should seek medical care immediately if you develop any of the following symptoms:
- Chest pains, shortness of breath, or if there is swelling of your ankles and feet, which may be symptoms of heart problems
- Difficulty breathing, including shortness of breath (dyspnea) at rest or with activity or a cough, rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung problems.
- Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis.
- Shortness of breath with everyday activities at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension.
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure
- Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells.

- A reaction to carfilzomib infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain
- Unusual bruising or bleeding, such as a cut that does not stop bleeding in a normal amount of time or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools.
- Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs).
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be a signs of liver problems, including liver failure.
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombocytopenic Thrombotic Purpura/Haemolytic Uremic Syndrome (TTP/HUS)
- Headaches, confusion, seizures, blindness, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as Posterior Reversible Encephalopathy Syndrome (PRES).

The following side effects have been seen in people who received carfilzomib. It is unknown if they were caused by carfilzomib, you may or may not experience these side effects:

- Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML).
- Tenderness or pain in the abdomen that gets more intense with motion or touch, abdominal bloating or distention, nausea or vomiting, diarrhea, constipation or the inability to pass gas which may be symptoms of swelling of the thin tissue that lines the inner wall of the abdomen and covers most of the abdominal organs
- Painful skin rash, Shingles (Herpes zoster)

Carfilzomib may impair ability to operate a car, other motorized vehicle, or machinery because of tiredness, dizziness, changes in blood pressure, or fainting.

HYDRATION RISKS (PREVENTION OF TLS)

There may be risks associated with over hydrating (having too much fluid in your body) so it is important to follow your doctor's instructions regarding how much water or other fluids you should drink. Over hydration may negatively affect the heart, lungs, and kidneys.

The known and potential risks for the standard chemotherapy drugs **Cyclophosphamide** and **Etoposide** associated with the study under investigation for your condition may include, but are not limited to:

- Likely (greater than 20% chance of occurring)
- Less Likely (1-19% chance of occurring)
- Rare but serious (less than 1% chance of occurring)

Risks and side effects related to Cyclophosphamide include those which are:

Likely *(occurs in more than 20 out of 100 patients)*

- Loss of appetite
- Nausea
- Vomiting
- Fewer white blood cells in the blood.
- A low number of white blood cells may make it easier to get infections.
- Hair loss
- Decreased ability of the body to fight infection
- Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children

Less Likely *(occurs in 1–19 out of 100 patients)*

- Abdominal pain
- Diarrhea
- Fewer red blood cells and platelets in the blood
- A low number of red blood cells may make you feel tired and weak.
- A low number of platelets may cause you to bruise and bleed more easily.
- Bleeding and inflammation of the urinary bladder
- Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children

Rare but Serious (occurs in less than 1 out of 100 patients)

- Heart muscle damage which may occur with very high doses and which may be fatal
- Abnormal heart rhythms
- Damage and scarring of lung tissue which may make you short of breath
- A new cancer or leukemia resulting from this treatment.
- Damage or scarring of urinary bladder tissue
- Severe allergic reaction which can be life-threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
- Infertility which is the inability to have children
- Infections
- Slow healing of wounds
- Temporary blurred vision
- Skin rash
- Darkening of areas of the skin and finger nails
- Nasal stuffiness with IV infusions
- Abnormal hormone function which may lower the level of salt in the blood

Risks and side effects related to <u>Etoposide</u> include those which are:

Likely *(occurs in more than 20 out of 100 patients)*

- Nausea and vomiting
- Hair loss
- Fewer red and white blood cells and platelets in the blood
- A low number of red blood cells can make you feel tired and weak
- A low number of white blood cells can make it easier to get infections

Less Likely *(occurs in 1–19 out of 100 patients)*

- Loss of appetite
- Rashes
- Diarrhea
- Pain in the abdomen
- Mouth sores
- A low number of platelets causes you to bruise and bleed more easily
- A feeling of weakness or tiredness

Rare but Serious (occurs in less than 1 out of 100 patients)

- Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
- Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid
- Decreased blood pressure during the infusion which may require treatment
- Damage to the liver
- Severe allergic reaction which can be life-threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
- A new cancer or leukemia resulting from this treatment
- Severe rashes which can result in loss of skin and damage to mucous membranes
- Tingling sensation or loss of sensation in fingers or toes
- Chest pain
- The finger or toe nails may loosen from their nail beds
- A feeling of extreme tiredness or weakness
- Inflammation of the vein through which the medication was given
- Muscle spasms

The known and potential risks for **IT Cytarabine** and **IT Methotrexate** associated with the study under investigation for your condition may include, but are not limited to:

- Likely (greater than 20% chance of occurring)
- Less Likely (1-19% chance of occurring)
- Rare but serious (less than 1% chance of occurring)

Risks and side effects related to IT Cytarabine include those which are:

Likely *(occurs in more than 20 out of 100 patients)*

- Nausea and vomiting
- Fever
- Headache

Less Likely *(occurs in 1–19 out of 100 patients)*

- Meningitis symptoms
- Stiff neck
- Increased white blood cells in spinal fluid

Rare but Serious (occurs in less than 1 out of 100 patients)

- Rash
- Fatigue
- Convulsions
- Weakness
- Decreased blood cells
- Unsteadiness
- Brain damage
- Inability to walk
- Loss of eye-sight

Risks and side effects related to <u>IT Methotrexate</u> include those which are:

Likely *(occurs in more than 20 out of 100 patients)*

- Nausea and vomiting
- Headache

Less Likely *(occurs in 1–19 out of 100 patients)*

- Fever
- Vomiting
- Meningitis symptoms
- Stiff neck
- Increased white blood cells in spinal fluid
- Thinking difficulty
- Learning disability

Rare but Serious (occurs in less than 1 out of 100 patients)

- Rash
- Severe allergic reaction
- Seizures
- Fatigue
- Confusion
- Back pain
- Bleeding around brain (risk > with platelet counts < 20,000)
- Decreased blood cells
- Unsteadiness
- Head/face weakness or decreased sensation
- Inability to walk
- Speech disorders
- Pain in the legs
- Bladder dysfunction
- Brain damage

<u>UNKNOWN RISKS OF COMBINATION</u>

As this is a new drug combination, side effects that are not yet known may also occur. The side effects of the combination of cyclophosphamide, etoposide and carfilzomib may be mild or could be severe enough to be life-threatening or cause death. You will be watched closely for side effects, and the drug will be stopped if unwanted or serious side effects develop.

<u>POSSIBLE RISKS AND DISCOMFORT ASSOCIATED WITH DRAWING BLOOD</u>

During this study, small amounts of blood will be drawn from a vein and used for tests that allow your study doctors to see how you are doing. Drawing blood may cause pain where the needle is inserted, and there is a small risk of bruising or infection at the place where the needle is inserted. Some people experience dizziness, upset stomach, or fainting when their blood is drawn. Topical medications (such as EMLA, a numbing cream) may be used to help make blood draws more comfortable.

POSSIBLE RISKS RELATED TO STUDIES FOR TUMOR ASSESSMENT

Your cancer will be assessed by physical examination, CT scans, MRI scans, PET scans, and/or MIBG scans as needed. You may also need a bone marrow aspirate and biopsy for assessment. The possible risks and discomfort associated with each of these are reported below.

POSSIBLE RISKS AND DISCOMFORT ASSOCIATED WITH SCANS

CT scan: Although the scanning itself causes no pain, there may be some discomfort from having to remain still for several minutes. If you have a hard time staying still, are claustrophobic (fear of tight spaces), or have chronic pain, you may find a CT examination to be stressful. You may need to take an oral medication to relax or possibly be given medications through an intravenous line in your hand or arm which causes a brief sleep (like an "anesthetic"). Your study doctor will discuss these drugs with you if you require them.

MRI scan: There are risks associated with MRI scans. If you are claustrophobic, the procedure may cause anxiety. You may need to take an oral medication to relax or possibly be given medications through an intravenous line in your hand or arm which causes a brief sleep (like an "anesthetic"). Your study doctor will discuss these drugs with you if you require them.
MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time (15-60 minutes) while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling. Some prostheses (man-made body parts) or implants contain metals that are unsafe in the MRI room; therefore, it is important that your study team know of all implants, prosthetic devices (such as pacemaker), piercings, metal plates, pins or any other type of metal that you may have in your body. Study personnel will ask questions to make sure you can safely have an MRI scan. Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Intravenous (IV) contrast: As part of a CT or MRI scan, you may be given an oral pill or an intravenous injection of dye in order to help see your organs or tumors on the radiology images. If you receive the dye through an intravenous line, you will feel a slight pin prick when the needle is inserted into your vein. You may have a warm, flushed sensation during the injection of the contrast materials and a metallic taste in your mouth that lasts for a few minutes. Some other risks associated with this contrast agent include mild nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. Some people may develop allergic symptoms (for example, hives, itching, difficulty breathing) and, in very rare cases, anaphylactic shock (low blood pressure, with loss of consciousness, severe loss of body fluid that can lead to shock or death). In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function. Prior to study entry, your study doctor will run tests to determine if your kidneys are working properly to make sure that the contrast agent is safe for you. It has been observed that deposits of Gadolinium-based contrast agent (GBCA) remain in the brains of some people who undergo four or more contrast enhanced MRI scans, long after the last administration. It is not yet known whether these Gadolinium deposits are harmful or can lead to adverse health effects. You should talk to the study doctor if you have any questions about the use of GBCAs with MRIs.

Radiation risks associated with scans: While you are in this research study, CT scans, PET/CT scans, and/or other tests that use X-rays or radiation may be used to evaluate your disease. You will be exposed to radiation from CT scans approximately every 6 weeks, which is similar to what you would receive as standard of care. This is considered to be a medically acceptable dose of radiation, which carries a low level of risk (for example, of developing another cancer in the future). Since the effects of radiation can build up over time, it is important to know of your past radiation exposure. If you have been exposed to radiation through CT scans, X-rays, or other means in the past 12 months, please inform study personnel. If it is determined that your prior radiation exposure exceeds current guidelines, it is possible that you will not be allowed to participate in this study. The potential risks of radiation should be weighed against the benefits that you may gain from participating in this trial and should be discussed with your doctor.

Risks of an FDG-PET scan: The risks with a PET scan are very minimal. The amount of radiation is very low and the FDG degrades quickly so that no detectable radioactivity is present after several hours. Any remaining FDG in your body is removed from the body through urine. Family members are not at risk for exposure since more than 90% of the radioactivity has left the body or decomposed before you have left the cancer clinic.

MIBG scan risks: The possible side effects of this scan include damage to the thyroid gland if potassium iodide drops are not taken as directed, pain or infection from the IV injection and allergic reaction to the radioactive iodine injection.

POSSIBLE RISKS AND DISCOMFORT ASSOCIATED WITH BIOPSIES

If you do not have tissue from a prior biopsy or tumor excision, a small sample of your tumor tissue will need to be obtained by biopsy. Risks associated with biopsies include pain, redness, swelling, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site.

POSSIBLE RISKS AND DISCOMFORT ASSOCIATED WITH BONE MARROW ASPIRATE AND BIOPSY

You may need a bone marrow aspirate and/or biopsy for tumor assessment on this study. During a bone marrow biopsy, there may be some discomfort during and after collection of the sample. You may experience pain, bleeding and swelling. Numbing medicine will likely be given with a syringe into the skin and tissues near the site of the bone marrow biopsy. There may be an increased risk of developing an infection at the sample site.

LUMBAR PUNCTURES RISKS ("L.P.S", "SPINAL TAPS")

If you have leukemia, you may be familiar with spinal taps since they were done during your initial therapy. Whether you decide to participate or not in this study, additional spinal taps may need to be done to give medicines which are necessary to prevent the leukemia from spreading to the spinal fluid. The medicines called cytarabine or methotrexate may be injected into your spinal canal while you are having a lumbar puncture. This way of giving medicine is called "intrathecal" or IT. Many children receive some form of sedation or anesthesia during this procedure. Approximately 1 teaspoon of spinal fluid will be withdrawn prior to injection of the medicine (cytarabine or methotrexate). Spinal taps are painful and may cause headaches.

WHAT ARE THE REPRODUCTIVE RISKS?

The treatment on this study can affect your unborn child. This study may also involve risks to an unborn child or fetus that currently are unknown or unforeseeable. A rare, but serious risk for Cyclophosphamide is the inability to have children (infertility). A rare, but serious risk for Etoposide is the absence or decrease of monthly periods which may be temporary or permanent and which may decrease the ability to have children.

If you are a female who could get pregnant, you must have a pregnancy test before you join this study. The results of all pregnancy tests will be shared with you. If you are a child on this study, the results of your pregnancy test will be shared with your parents. You will have a pregnancy test prior to each treatment cycle.

Abstinence is the best way to prevent pregnancy. However, if you are sexually active and are at risk of getting pregnant, or at risk of getting someone pregnant, you and your partner(s) must use contraception beginning at study enrollment and continuing until 1 month after the last dose of the investigational product. Below are some effective forms of birth control.

Methods of Birth Control
Any method of birth control can fail. Forms of contraception that are known to work can be called primary and secondary forms of contraception.

If a primary form and a secondary form of birth control are used, the risk of pregnancy is highly reduced. It is highly recommended that patients who are sexually active use one primary and one secondary form at the same time.

Primary Forms	Secondary Forms
Combination oral contraceptives (birth control pill)	Male latex condom with or without spermicide
Injectable (Depo-Provera) (shot)	Diaphragm with spermicide
Intrauterine device (IUD)	Cervical cap with spermicide
Vaginal ring (Nuvaring)	Vaginal sponge (contains spermicide)
Transdermal patch (Ortho Evra)	
Implants (Nexplanon)	

Not every form of birth control is appropriate for every individual, and individual patients need to discuss which methods are medically appropriate for them with their gynecologist. Lucile Packard Children's Hospital has a Pediatric Gynecology Clinic. They can be reached at (408) 637-5959 or your study doctor can assist you in contacting them.

You need to notify your study doctor right away if you change your form of birth control or if pregnancy does occur during treatment.

POTENTIAL BENEFITS

Are there benefits to taking part in this study?
If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with relapsed/refractory tumors or leukemia in the future. We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

What other options are there?
You do not have to participate in this research study to receive treatment for your cancer. Before signing this informed consent document, the study doctor will talk to you about other treatments or therapies that are available for you. These other treatments/therapies may already be approved for your condition or there may be other study drugs available in different research studies. There may be different opinions as to whether these other treatments would be good for you. It is important that you talk to the study doctor about the benefits and risks of all treatment options.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

When informed of this new information, if you agree to continue in the study, you or your legally authorized representative will be asked to sign an updated consent form.

ClinicalTrials.gov

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

As part of this research study, your study doctor, nurses, and other Study Site staff will collect and record medical and personal information about you, such as information about your general health, how you have responded to the study drug, any side effects you may have experienced, and the results of any tests performed during the study. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of Carfilzomib with Cyclophosphamide and Etoposide; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required. The individuals associated with this study who will receive your private health information include:

- Your study physician and their research team
- Phoenix Children's Hospital and the Phoenix Children's Hospital Institutional Review Board (IRB)
- The Department of Health and Human Services including but not limited to the Food and Drug Administration and the Office of Human Research Protections
- The following research sponsors: The Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) and Amgen, who is providing carfilzomib
- Every research site for this study, including Memorial Sloan Kettering Cancer Center and their research support staff (for example, research study assistant) and medical staff at each location
- The (POETIC) Data and Coordinating at Stanford University
- Phoenix Children's Hospital Laboratory, Laboratory Corporation of America, Sonora Quest Laboratories
- The National Cancer Institute and/or the National Institutes of Health
- The following laboratories who will be analyzing the research samples:
  - Dr. Aru Narendran
    University of Calgary
    Laboratory HM336 AN
    2500 University Drive NW
    Calgary, AB T2N1N4 Canada

  - Phoenix Children's Hospital Lab
    Biorepository, 3rd Floor Main Lab
    1919 E Thomas Road
    Phoenix, AZ 85016

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law will protect you in these ways:

- Health insurance companies and group health plans may not ask for your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information to make decisions on whether to cover you, what your plan will or will not cover, or how much you pay.

- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you when setting the terms of your employment.

All health insurance companies and group health plans must follow this law since May 21, 2010. All employers with 15 or more employees must follow this law since November 21, 2009.

This Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. There are limited exceptions, such as for military personnel, in which these protections may not apply.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to assess the effects, good and/or bad, of treatment with a new combination of drugs: cyclophosphamide, etoposide, and carfilzomib have on you and your cancer. Information from this study will be submitted to the sponsor and the FDA. If you sign this consent form, you give permission to use or disclose (share) your health information that identifies you only for the purposes of this research study and for research directly related to pediatric cancer, the use of carfilzomib in disease therapy, and/or the development of tests that help with detection or understanding of your disease. You do not have to sign this consent form, but if you do not, you may not take part in this research study.

Efforts will be made to keep your personal information private. Your name will not be used in any publications resulting from the research. Identifying information will be on file at the POETIC Data and Coordinating Center. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as Representatives of the Food and Drug Administration (FDA) and National Cancer Institute (NCI).

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Norman Lacayo, MD, 1000 Welch Road, Suite 300, Palo Alto, CA 94304

What Personal Information Will Be Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your name, address, phone number(s), date of birth, age, sex, race and medical record number (MRN). During the study, researchers will also obtain information about your medical history and diagnoses, current and past medications or therapies, physical examination results, laboratory tests, results of procedures and medical reports (such as pathology reports).

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Dr. Norman Lacayo
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services

- The Food and Drug Administration
- POETIC's study monitors and representatives
- POETIC collaborators and licensees (people and companies who partner with POETIC)
- Regulatory health authorities (government agencies involved in keeping research safe for people)

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will expire 12/31/2110 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

_____
Print Name of Adult Participant

OR

_____ _____
Signature of Legally Authorized Representative Date

_____

Printed name of LAR

_____

Description of Representative's Authority to Act for Subject

CONSENT FOR OPTIONAL STUDIES FOR RESEARCH

You can choose to take part in this clinical trial without taking part in the following tests. The results will not be used to make any treatment decisions on the main study, and will not be given to you or your doctor. The results may help to improve treatments for cancer in the future. No matter what you decide, your care will not be affected. Following each specimen description below, there is a place for you to record your decision about taking part in these optional tests.

If you decide now that your specimens can be used for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Any specimens that may have been collected will be destroyed.

Researchers will obtain blood (up to 2 teaspoons) and bone marrow samples (up to 1 teaspoon) to be used for several research tests which would not be done if you were not being treated with the combination cyclophosphamide, etoposide and carfilzomib. You will not be charged for these tests. These tests are optional.

The following tests will be done as part of this study. These tests are not part of standard care, and will only be done if you agree to them.

Optional Biology Studies

I agree to have my blood samples obtained and sent to Dr. Aru Narendran in Alberta, Canada, for research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.
Mark your choice and initial and date

☐ **I agree** to have blood samples sent for biology studies. _____
Initial and date

☐ **I do NOT agree** to have blood samples sent for biology studies. _____
Initial and date

I agree to have the following samples sent to Phoenix Children's Hospital Lab in Phoenix, Arizona, for research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.

Blood Samples

Mark your choice and initial and date

☐ **I agree** to have blood samples sent for biology studies. _____
Initial and date

☐ **I do NOT agree** to have blood samples sent for biology studies. _____
Initial and date

Bone Marrow Samples

Mark your choice and initial and date

☐ **I agree** to have bone marrow samples sent for biology studies. _____ Initial and date

☐ **I do NOT agree** to have bone marrow samples sent for biology studies. _____ Initial and date

Tumor Sample, if available

Mark your choice and initial and date

☐ **I agree** to have tumor sample sent for biology studies. _____ Initial and date

☐ **I do NOT agree** to have tumor sample sent for biology studies _____ Initial and date

CONSENT FOR USE OF SPECIMENS (OR INFORMATION) FOR FUTURE RESEARCH

How will your specimens be collected?

If you consent to the above listed optional biology studies, we would like to keep some of the bone marrow and blood that is left over for future research. If you agree, these specimens will be kept and may be used in future research.

Who will keep your specimens?

Dr. Aru Narendran will maintain blood samples at The University of Calgary, Laboratory HM336 AN, 2500 University Drive NW, Calgary AB T2N1N4 Canada.

Blood, bone marrow, and tumor samples will be maintained at the Phoenix Children's Hospital, Biorepository 3rdFloor Main Lab , 1919 E Thomas Road, Phoenix, Arizona 85016

What type of research will be done with your specimen?

Your samples will be used to study the type of cancer you have. It may also be used for future research on other types of cancers or illnesses.

How will we keep your information private?

If and when we do research with your specimens, reports will not be put into your health record. We will not send reports to you or your doctor. The research will not change your care. Sometimes specimens are used to look at diseases passed on in families (genetic diseases). Even if your specimens are used for this kind of research, the results will not be put in your health records. The only people who will be able to see your research records will be people doing this study who are listed in the HIPAA Authorization form.

In the future, people who do research may need to know more about your health. While reports about your health may be given to Dr. Narendran and/or Phoenix Children's Hospital Lab, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

We will do our best to make sure that your personal information will be kept private. However, there is a risk that information about you may get out by accident. If this happens, there is a chance you could have a problem getting insurance or a job. If information about family relationships comes out (such as paternity), family relationships or social standing may be hurt. However, we will be very careful to prevent information that identifies you from getting to people who are not supposed to get it.

What are the benefits of participating?
The benefits of research using specimens include learning more about what causes diseases, how to prevent them, and how to treat them. The research that may be done with your specimens is not meant to help you. It might help people who have diseases in the future.

What are the risks of participating?
Having your blood drawn may cause mild bruising, swelling, and pain at the site at which the blood was taken. There is also a very small risk of infection at the site within the few days after the blood draw.

The bone marrow test may be painful. There is also a small risk of infection or bleeding. The pain normally lessens within minutes to hours.

Will you receive compensation?
No, you will get no money for giving your specimens for this research. Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Your Participation is Voluntary
The choice to let us keep specimens for future research is up to you. No matter what you decide to do, it will not affect your care. If you change your mind, any specimens that remain at The University of Calgary or Phoenix Children's Hospital Lab will no longer be used for research and/or destroyed. We will also contact Dr. Narendran and/or Phoenix Children's Hospital Lab, who received your specimens, and ask that they return or destroy any unused specimens.

To withdraw from this study or have your specimens withdrawn, you must write to Dr. Norman Lacayo, 1000 Welch Rd, Palo Alto CA 94304, or you may ask a member of the research team to give you a form to withdraw your authorization. If you withdraw your authorization, you are still able to continue to participate in this study. You will still receive all the medical care and benefits for which you are otherwise eligible.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, check the appropriate response, and initial your decision. If you have any questions, please talk to your doctor, or call the IRB. No matter what you decide to do, it will not affect your care.

I agree to have my blood samples kept by Dr. Aru Narendran with the University of Calgary in Alberta, Canada for future research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.

Mark your choice and initial and date

☐ **I agree** to have blood samples kept for future research. _____
Initial and date

☐ **I do NOT agree** to have blood samples kept for future research _____
Initial and date

I agree to have my blood samples kept by Phoenix Children's Hospital Lab in Phoenix, Arizona for future research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.
Mark your choice and initial and date

☐ **I agree** to have blood samples kept for future research _____
Initial and date

☐ **I do NOT agree** to have blood samples kept for future research _____
Initial and date

I agree to have my bone marrow samples kept by Phoenix Children's Hospital Lab in Phoenix, Arizona for future research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.
Mark your choice and initial and date

☐ **I agree** to have bone marrow samples kept for future research _____
Initial and date

☐ **I do NOT agree** to have bone marrow samples kept for future research _____
Initial and date

If available, I agree to have my tumor samples kept by Phoenix Children's Hospital Lab in Phoenix, Arizona for future research studies that will not directly impact my treatment. The results of these research studies may benefit future cancer patients.
Mark your choice and initial and date

☐ **I agree** to have tumor samples kept for future research.
_____Initial/Date

☐ **I do NOT agree** to have tumor samples kept for future research.
_____Initial/Date

CONSENT FOR GENETIC RESEARCH PARTICIPATION

Invitation to Participate
Federal regulations state that researchers cannot collect or perform research on your genetic samples unless the investigator has gained your permission and informed consent. True voluntary informed consent contains three features: information, your ability to understand the information, and your voluntary agreement to take part in the research. Having enough information is important for your decision to take part in research (or not). Prior to agreeing to genetic research, you must understand the nature of your participation, and the potential risks and benefits. Finally, an agreement to take part in research is valid only if it is voluntarily given.

Why is this Study Being Done?
Some genes for cancer have already been identified, but new discoveries are being made and genes we did not know about may be identified in the future. The purpose of this genetic research is to allow Phoenix Children's Hospital Lab to collect genetic samples and then potentially use them in the future to study genes that may be involved in cancer.

Your genetic sample and results of research done on your genetic sample will be considered the property of the Phoenix Children's Hospital Lab and may be shared, as part of commercial agreements, with private companies. As part of such activity, Phoenix Children's Hospital Lab may obtain, alone or in partnership with private companies, patents or other legal licenses relating to possible diagnostic or treatment methods, which may lead to financial benefit. They do not have plans for the research participants to share in this economic benefit. You do not waive any legal rights by signing this document.

What is Involved in this Genetic Research?
If you choose to take part in this genetic research, Phoenix Children's Hospital Lab will be provided with residual (leftover) genetic samples taken for routine tests during the study, including blood, bone marrow and tumor tissue samples, if available. Additionally, a test called a buccal (cheek) swab will be performed. This test requires a cotton swab to be rubbed on the inside of your mouth on the cheek area.

In addition to your genetic samples, Phoenix Children's Hospital Lab will also be provided with your protected health information. However, any health information provided to Phoenix Children's Hospital Lab will not include information that could be used to directly identify you (such as your name or birth date); because this information will have been replaced by the investigator with a unique identification (ID) number. Phoenix Children's Hospital Lab will not be able to link this ID number with your identity.

How long will my samples be kept?
Your samples will be stored until they are used for the research described in this document or destroyed by Phoenix Children's Hospital Lab. Samples may be kept indefinitely.

What are the risks of participating?
All samples will be made anonymous (stripped of all personal identifiers, such as name and birth date, that could be used to link them back to an individual). This will protect your identity and eliminate the possibility of an accidental breach of privacy and confidentiality.

In the rare event that an invasion of privacy or breach in confidentiality occurred, there is a small risk of social, economic, psychological, or other unknown risks associated with your participation; this could result in embarrassment, stigma, and financial or mental stress.

What are the benefits of participating?
You will not benefit directly by taking part in this genetic research. Information learned from the genetic research may help patients with cancer in the future.

If you agree to take part in this study, you will <u>not</u> be notified when the genetic research takes place, and you will <u>not</u> be provided with the results of the research because your samples hold no direct link to your identity.

A possible risk of not being provided with your research findings includes being unaware of the need for treatment.

Your Participation is Voluntary
You may stop taking part in this study at any time. If you decide to stop taking part in the study, must notify Dr. Norman Lacayo of your decision. Once the investigator is notified, no new residual (leftovers) samples will be collected or provided to Phoenix Children's Hospital Lab. Additionally, if any samples have already been collected and provided to Phoenix Children's Hospital Lab, they will destroy these samples if they can be linked to you. However, if research has already been conducted on the samples, the Sponsor will keep the results of that research.

Making Your Choice
Please read each sentence below and think about your choice. After marking your selection, please initial where indicated. If you have any questions, please talk to your doctor, or call the IRB. No matter what you decide to do, it will not affect your care.

Mark your decision and initial and date

☐ I will allow genetic testing for study purposes only.

_____
Initial and date

☐ I will NOT allow genetic testing for study purposes

_____
Initial and date

FINANCIAL CONSIDERATIONS

What are the costs?
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

Sponsor
POETIC and Amgen are providing financial support and/or material for this study.

The National Institutes of Health are providing some financial support for the facility and staff where part or all of the study is taking place.

Is there payment for participating?
You will not be paid for your participation in this research study.

COMPENSATION for Research-Related Injury

What happens if i am injured?
All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.
You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, Dr. Norman Lacayo at (650) 497-8953. You should also contact him at any time if you feel you have been hurt by being a part of this study.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650) 723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and

- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

_____
Printed name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Printed name of Legally Authorized Representative (LAR)

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

_____ _____
(If available) Signature of Other Parent or Guardian Date

_____
Authority to Act for Participant

_____
Printed name of Legally Authorized Representative (LAR)

The IRB determined that the permission of two parents is recommended in accordance with 21 CFR 50.55 unless one parent is deceased, unknown, incompetent, not reasonably available, or only one parent has legal responsibility for the care and custody of the child. *Not reasonably available* means that the other parent is not present during the consenting process, or will not be available prior to the start of research procedures.

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of Witness Date

_____
Printed name of Witness
(e.g., staff, translator/interpreter, family member)

- *Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.*
- *The English consent form (referred to as the "Summary Form" in the regulations):*
  - *Must be signed by the witness AND the Person Obtaining Consent (POC).*
  - *The non-English speaking participant/LAR does not sign the English consent.*
  - *The non-English speaking participant/LAR should not sign the HIPAA participant line*
  - *If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.*